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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/714,068

11/14/2003

Meng Yang

312762002710

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25225 7590 05/18/2010

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EXAMINER

WOOLWINE, SAMUEL C

ART UNIT

PAPER NUMBER

1637

MAIL DATE

DELIVERY MODE

05/18/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/714,068	Applicant(s) YANG ET AL.	
	Examiner SAMUEL C. WOOLWINE	Art Unit 1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 April 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 37 and 39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 37 and 39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>04/19/2010</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/09/2010 has been entered.

Claims 37 and 39 are pending in the application. The rejections made in the Office action mailed 12/09/2009 under section 103 are withdrawn in view of the amendment to each claim requiring "internal organ". While the cited references as a whole may have suggested such, there were no working examples indicating that GFP expression could be observed in an internal organ of a live, unrestrained, mobile mammal. While Okabe indicates that intact mice were fluorescent, and that various internal organs of the mice were also fluorescent (figure 1, e.g.), Okabe did not discuss whether the fluorescence of the internal organs could be observed from the outside. Presumably the skin of the mice was fluorescent, so it may not have been possible to discern whether fluorescence from the internal organs was observable in intact mice. In any event, it cannot be concluded whether fluorescence from an internal organ could be seen through the skin.

New grounds of rejection are set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims have been amended to recite an animal "which expresses a green or blue fluorescent protein in an internal organ". However, the claim later recites "observing the presence, absence or intensity of the fluorescence...at various locations in said animal". There is an inconsistency here between "an internal organ" and "various locations". If the animal only expresses the fluorescent protein in "an internal organ", how is one to observe fluorescence "at various locations"? Either the animal should express the fluorescent protein "at various locations", or the observation should be made of said "internal organ".

In addition, claim 37 at first recites "a green or blue fluorescent protein", and then later refers to "said fluorophore" (which is a broader term than "fluorescent protein"). It is advised to replace "said fluorophore" with "said fluorescent protein".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Yang et al (PNAS 97(3):1206-11, February 1, 2000, cited on the IDS of 04/22/2004).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a [light generating protein] under the direction of a promoter of an*

Art Unit: 1637

endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the [light] generated by said [light generating protein] at various locations [see above: "sites of inflammation"] in said animal, and further suggests determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the [light] generated by said [light generating protein] at various locations [see above: "sites of inflammation"] in a control laboratory animal which expresses said [light generating protein] under the direction of said promoter of said gene, and further suggests comparing the expression of said promoter determined in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during

Art Unit: 1637

imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in observing the effects of potential anti-inflammatory compounds on, e.g., E-selectin promoter expression, as suggested by Contag, at sites such as an internal organ, using green fluorescent protein instead of luciferase?

Yang taught whole body optical imaging of mice expressing GFP in various internal organs (e.g. abstract: "Whole-body optical images showed metastatic lesions in the brain, liver and bone of B16F0-GFP that were used for real time, quantitative measurement of tumor growth in each of these organs."). See also figure 5. This indicates it was within the skill of the art to visualize internal organs expression GFP in live mice (a non-human mammal) in real-time.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GFP taught by Yang in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of

Art Unit: 1637

studying potential anti-inflammatory compounds at sites of inflammation in internal organs.

As Contag taught luciferase, yellow fluorescent protein and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the GFP taught by Contag in place of the luciferase, since Yang taught (page 1206, column 2, 2nd paragraph: "However, luciferase enzymes transferred to mammalian cells require the exogenous delivery of their luciferin substrate, an essentially impractical requirement in an intact animal." In contrast, Yang taught of using GFP (page 1210, first paragraph of "Discussion"): "No contrast agents or other compounds or treatment need to be administered to the animals; only blue light illumination is necessary."

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Yang et al (PNAS 97(3):1206-11, February 1, 2000, cited on the IDS of 04/22/2004).

Lin taught the creation of genetically modified zebrafish expressing green fluorescent protein (column 7, line 11: "A preferred reporter protein that can be directly detected is the green fluorescent protein (GFP).").

Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the expression of the reporter protein in fish with a mutation to those without the mutation, the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed." By "mutations can be introduced into strains of transgenic fish", one of skill in the art would have understood that, in order to introduce the mutation to a strain of fish, the mutation would have to be introduced into the germ line (otherwise there would be one fish, not a strain, with the mutation in one cell, which would not have been realistically suitable for "comparing the expression of the reporter protein in fish with a mutation to those without the mutation").

Lin did not teach that the animals were non-human mammals, or that they were not restrained during observation.

Contag taught imaging light generating compounds including yellow and green fluorescent proteins (see abstract; column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in substituting mice expressing GFP in place of the fish expressing GFP in the method taught by Lin, and to observe GFP expression in internal organs?

Yang taught whole body optical imaging of mice expressing GFP in various internal organs (e.g. abstract: "Whole-body optical images showed metastatic lesions in the brain, liver and bone of B16F0-GFP that were used for real time, quantitative measurement of tumor growth in each of these organs."). See also figure 5. This indicates it was within the skill of the art to visualize internal organs expression GFP in live mice (a non-human mammal) in real-time.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute mice for fish in the method of Lin. One would

Art Unit: 1637

have been motivated to do so because mice were a well-known experimental animal. Furthermore, this would have allowed study of, for example, lung-specific gene expression, which obviously would not have been possible using fish as a model organism. Hence, mice would have allowed one to study gene expression patterns in the lungs in response to various mutations when practicing Lin's method.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Tan et al (US 6,251,384).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a [light generating protein] under the direction of a promoter of an endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the [light] generated by said [light generating protein] at various locations [see above: "sites of inflammation"] in said animal, and further*

Art Unit: 1637

suggests *determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the [light] generated by said [light generating protein] at various locations [see above: "sites of inflammation"] in a control laboratory animal which expresses said [light generating protein] under the direction of said promoter of said gene*, and further suggests *comparing the expression of said promoter determined in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression* (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

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This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in observing the effects of potential anti-inflammatory compounds on, e.g., E-selectin promoter expression, as suggested by Contag, at sites such as an internal organ, using green fluorescent protein instead of luciferase?

Tan taught that GFP producing tumors could be excised and observed for fluorescence (column 3, lines 9-14). Tan also taught that sometimes it was not necessary to remove organ tissues; rather the fluorescence could be visualized in the whole animal by real time fluorescence optical tumor imaging (column 3, lines 15-18). At column 5, line 30, Tan stated: "In some cases the tumors are sufficiently bright that opening the animal is unnecessary—they can be seen directly through the skin." In a working example involving mice, Tan disclosed (column 12, lines 13-15): "In some cases, abdominal opening is unnecessary as the intraperitoneal tumors can be visualized through intact skin."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GFP taught by Tan in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation in internal organs.

As Contag taught luciferase and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the GFP in place of the luciferase, since GFP does not require any additional compounds (such as luciferin) to be administered to the animals in order to produce fluorescence.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Tan et al (US 6,251,384).

Lin taught the creation of genetically modified zebrafish expressing green fluorescent protein (column 7, line 11: "A preferred reporter protein that can be directly detected is the green fluorescent protein (GFP).").

Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the

Art Unit: 1637

expression of the reporter protein in fish with a mutation to those without the mutation, the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed." By "mutations can be introduced into strains of transgenic fish", one of skill in the art would have understood that, in order to introduce the mutation to a strain of fish, the mutation would have to be introduced into the germ line (otherwise there would be one fish, not a strain, with the mutation in one cell, which would not have been realistically suitable for "comparing the expression of the reporter protein in fish with a mutation to those without the mutation").

Lin did not teach that the animals were non-human mammals, or that they were not restrained during observation.

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute mice for fish in the method of Lin. One would have been motivated to do so because mice were a well-known experimental animal. Furthermore, this would have allowed study of, for example, lung-specific gene expression, which obviously would not have been possible using fish as a model organism. Hence, mice would have allowed one to study gene expression patterns in the lungs in response to various mutations when practicing Lin's method.

Response to Arguments

Applicant's arguments with respect to claims 37 and 39 have been considered but are moot in view of the new ground(s) of rejection. Each of the references Yang et al and Tan et al provide a reasonable expectation of success in observing GFP fluorescence in internal organs within intact, living mice.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Examiner, Art Unit 1637